EXTENDED REPORT

# The H63D variant in the *HFE* gene predisposes to arthralgia, chondrocalcinosis and osteoarthritis

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**Objectives:** To investigate the relation between the *HFE* C282Y and H63D variants with arthralgia and joint pathology in the population-based Rotterdam Study.
**Methods:** From a cohort of 7983 people aged 55 years and over, 2095 randomly drawn subjects were genotyped for C282Y and H63D variants. We compared the frequency of arthralgia, and the presence of chondrocalcinosis, osteophytes, joint space narrowing and radiographic osteoarthritis in hand, hip and knee joints, and Heberden's nodes in carriers of *HFE* variants with that in non-carriers.
**Results:** Overall, there was a significantly higher frequency of arthralgia (odds ratio 1.6; 95% CI 1.0 to 2.6), oligoarthralgia (2.3; 1.2 to 4.4) and Heberden's nodes (2.0; 1.1 to 3.8) in H63D homozygotes compared with non-carriers. In subjects aged 65 years or younger, H63D homozygotes had significantly more often polyarthralgia (3.1; 1.3 to 7.4), chondrocalcinosis in hip or knee joints (4.7; 1.2 to 18.5), and more hand joints with osteophytes ($6.1 \pm 1.0$ vs $4.4 \pm 0.3$), space narrowing ($2.8 \pm 0.5$ vs $1.0 \pm 0.1$), radiographic osteoarthritis ($4.4 \pm 0.7$ vs $2.0 \pm 0.2$) and Heberden's nodes (3.1; 1.3 to 12.8) than non-carriers. We found no relation of arthralgia or joint pathology to C282Y, but compound heterozygotes had a significantly higher frequency of arthralgia (2.9; 1.0 to 9.3), chondrocalcinosis in hip joints (6.5; 1.8 to 22.3), and an increased number of osteophytes in knee ($6.9 \pm 1.2$, n = 5 vs $2.4 \pm 0.1$) joints at a later age (>65 years).
**Conclusions:** The *HFE* H63D variant may explain, at least in part, the prevalence of arthralgia in multiple joints sites, chondrocalcinosis, and hand osteoarthritis in the general population.

Arthropathy affects up to 85% of patients with type I hereditary haemochromatosis,[1–6] seriously influencing their quality of life.[7] Hand, hip and knee joints are most often affected.[8–11] In patients with haemochromatosis, arthropathy may originate from a progressive degenerative arthritis initially presenting in hand joints,[9 10] but it can also originate from an inflammatory mediated condition like chondrocalcinosis,[9 10 12] or it may resemble rheumatoid arthritis,[8 9] accompanied by Heberden's nodes.[13] The main radiographic findings in haemochromatosis arthropathy are calcium crystal depositions, osteophytes and joint space narrowing.[9 10]

The *HFE* C282Y and H63D variants are the most common genetic factors involved in hereditary haemochromatosis.[5 14–16] Eleven per cent of Caucasians are carriers of C282Y, and 23% of the total population worldwide are carriers of H63D.[15] The risk of haemochromatosis is increased for C282Y homozygotes (4383-fold) or compound heterozygotes, that is carriers of both H63D and C282Y (32-fold).[15] Also, H63D homozygotes are estimated to have a sixfold increased risk of haemochromatosis, although their iron levels may be modestly increased.[15 17]

Findings on the relation between *HFE* variants and arthropathy are neither consistent nor conclusive. Some studies found no relationship between C282Y and self-reported arthropathy,[18] inflamed joints,[19] chondrocalcinosis[20 21] or subchondral arthritis.[20] Other studies reported a significant association between C282Y and chondrocalcinosis,[22] or late-onset hand osteoarthritis.[21] Few studies have addressed the role of H63D.[20 21] Most studies on the *HFE* gene variants were based on clinical samples, and were prone to selection bias.[23] Thus, the generalisability of these studies has been a matter of concern.[23] We have studied the *HFE* C282Y and H63D variants in the population-based Rotterdam Study.[24] The variants were studied in relation to arthralgia as well as joint pathology assessed from radiographs, including chondrocalcinosis in hip or knee joints, presence of osteophytes, joint space narrowing, radiographic osteoarthritis in hand, hip or knee joints, and Heberden's nodes. We also investigated the relationship between *HFE*, arthralgia and overall mortality.

## METHODS

### Population

This study was performed in the framework of the Rotterdam Study, a population-based cohort study of major chronic diseases in a large city in the Netherlands. The medical ethics committee of the Erasmus Medical Centre approved the study, and informed consent was obtained from all participants. The design and objectives of the study have been described elsewhere.[25] In brief, the study population consists of 7983 inhabitants aged 55 years or over living in the district of Ommoord in Rotterdam. Baseline examinations took place between 1990 and 1993 by means of a structured interview using a standardised questionnaire. In the Rotterdam Study, all participants have been followed since 1990, with information on the vital status of participants being obtained at regular intervals from municipal health authorities in Rotterdam. The data on hospital admissions and a corresponding diagnosis of haemochromatosis were retrieved from interviews with participants and from their general practitioners' medical records. Data on the disease conditions and mortality were available for all the participants. From the total cohort, 2095 randomly drawn subjects were genotyped for the *HFE* C282Y and H63D variants.

### Main outcome measures

In this study, the main outcome measures included arthralgia and osteoarthritis in hand, hip and knee joints at baseline examination between 1990 and 1993. At the baseline examination, participants were asked whether they had any pain in or around their joints. If yes, the study physicians questioned participants about the site and duration of joint complaints,

and asked whether they had received a medical diagnosis of joint or other diseases, or whether they were treated with any kind of pain medication or physiotherapy because of their joint complaints. At the study's research centre, study physicians examined the hands of all participants for the presence of Heberden's nodes, a common local form of osteoarthritis in the distal interphalangeal joints with inflammatory episodes that are associated with generalised osteoarthritis.[26 27] Within the randomly selected cohort (n = 2095), clinical data were available on the presence or absence of arthralgia for 2047 subjects and on Heberden's nodes for 1833 subjects.

The baseline anteroposterior radiographs of hip and knee joints of a random subset of the population were scored for the presence of chondrocalcinosis and radiographic osteoarthritis by two independent medical physicians who were trained by a musculoskeletal radiologist and a rheumatologist (J H); they were also blind to all information on participants as explained elsewhere.[28] The reliability of scoring for radiographic osteoarthritis in hip or knee joints has been explained elsewhere.[28] In brief, whenever the scores of the two assessors differed by more than one grade or when one assessor scored grade 1 and the other grade 2 or higher, one more consensus reading was carried out that was later confirmed by the musculoskeletal radiologist.[28]

The presence of osteophytes and space narrowing in the baseline anteroposterior and lateral oblique radiographs of hands were assessed in the distal and proximal interphalangeal joints, the interphalangeal joint of thumb, the metacarpophalangeal joints, the first carpometacarpal joints and the trapezoscaphoideal joints. Osteophytes were differentiated into three grades (small, moderate and large), while joint space narrowing was scored as either present or absent. Lateral deformity was defined as misalignment of at least 15°. Radiographic osteoarthritis in hand, hip and knee joints was graded (0–4) as proposed by Kellgren and Lawrence using the original atlas.[29] The diagnosis of radiographic osteoarthritis was considered for any joint with a Kellgren–Lawrence score of two or higher. The two assessors both independently scored a random subset of 205 radiographs for osteoarthritis in hand joints. The inter-observer reliability for Kellgren–Lawrence scores of the two assessors, expressed by kappa statistics, was as follows: DIP 0.60, PIPs 0.61, MCPs 0.63; and CMC1/TS 0.74. Within the randomly selected cohort, there were data available on the presence of chondrocalcinosis in hip or knee joints for 1132 subjects, on the presence of osteophytes, joint space narrowing and radiographic osteoarthritis in hand joints for 1274 subjects, in knee joints for 1112 subjects, and in hip joints for 1352 subjects. Finally, for H63D or C282Y homozygotes (n = 65), all radiographs at baseline and follow-up were re-examined for the presence of osteophytes, joint space narrowing, sclerosis, cyst formation, calcification, chondrocalcinosis in subchondral bone in hand, hip and knee joints and in spinal joints for disk degeneration, spondylophytes and calcification by a rheumatologist (JH) who was blind to the clinical data but knew of the subjects' *HFE* genotypes.

Blood samples were collected on the day of baseline examination by venepuncture. The *HFE* C282Y and H63D variants were genotyped as described elsewhere.[14]

### Data analysis

The extent of arthralgia was categorised into 4 groups: 0 for no arthralgia (the reference group), 1 for presence of pain in one, 2 for pain in two (oligoarthralgia), and 3 for pain in three or more (polyarthralgia) joint sites. The presence of osteophytes, space narrowing and radiographic osteoarthritis in hands joints was transformed to 3 independent quantitative traits by summing the number of joints with the corresponding condition. The *HFE* C282Y genotypes were modelled by assigning a value of 0, 1 or 2 for carriers of no (non-carriers), one (C282Y heterozygotes), or two (C282Y homozygotes) copies of this variant, respectively. The same procedure was done for H63D.

Genotype proportions were tested for Hardy–Weinberg equilibrium. Independent *t* statistics, ANOVA and $\chi^2$ tests were used for comparisons of means and frequencies. We performed cross-sectional analyses to estimate odds ratio with 95% confidence interval (95% CI). We used logistic regression analysis to test the association of C282Y or H63D with the risk of arthralgia overall and in different joint sites, chondrocalcinosis in hip or knee joints, or Heberden's nodes in both hands, and radiographic osteoarthritis in hip or knee joints. Univariate regression analysis was used to estimate the adjusted mean with the standard errors for the number of hand joints with osteophytes, joint space narrowing, or radiographic osteoarthritis by the *HFE* genotypes. For the study of mortality, we used a Cox proportional regression analysis. All analyses were adjusted for age and gender. Since a relation of C282Y heterozygosity to hand osteoarthritis was found in patients older than 65 years,[21] and since there may be differences in the aetiopathogenesis of early- and late-onset arthropathy,[30] we stratified our analysis by age using a cutoff point of 65 years. A two-sided $p<0.05$ was considered statistically significant.

## RESULTS

### Baseline characteristics

Table 1 presents the baseline characteristics of the participants. Subjects with arthralgia were more often female and users of pain medications ($p<0.001$). Genotype frequencies and baseline characteristics did not differ between those aged 65 years or younger and those older than 65 years, or between subjects who had data on genotype, clinical and radiographic findings compared with others (data not shown). In subjects with arthralgia, the number of painful joints for each person ranged from 1 to 10 (median = 2). Allele and genotype proportions were in Hardy–Weinberg equilibrium overall and also in those without arthralgia. The baseline characteristics did not differ across the *HFE* genotypes, except that H63D homozygotes aged 65 years or younger were significantly ($p = 0.02$) more often users of pain medications and physiotherapy than non-carriers (data not shown).

### *HFE* variants and arthralgia

Overall, H63D homozygotes had a significantly higher frequency of polyarthralgia (OR 1.6; 95% CI 1.0 to 2.6; $p = 0.05$) and oligoarthralgia (2.3; 1.2 to 4.4; $p = 0.01$) compared with non-carriers. The frequency of arthralgia was not higher in C282Y or H63D heterozygotes compared with non-carriers. Figure 1 presents the analysis stratified by age. H63D homozygotes aged 65 years or younger had arthralgia significantly ($p = 0.01$) more often than non-carriers. Figure 2A shows that H63D homozygotes had a significantly increased risk of arthralgia in hands ($p = 0.006$), in hips ($p = 0.05$) and in knees ($p = 0.03$). In those older than 65 years, the frequency of arthralgia did not differ by *HFE* genotypes (figs 1 and 2B).

### *HFE* variants and chondrocalcinosis

Overall, there was no significant difference in the frequency of chondrocalcinosis in hip or knee joints in the *HFE* genotypes. When stratifying by age (table 2), H63D homozygotes aged 65 years or younger had a significantly ($p = 0.02$) higher frequency of chondrocalcinosis compared with non-carriers.

### *HFE* variants and radiographic osteoarthritis

Overall, the number of joints with osteophytes in the hands increased significantly with the numbers of H63D variant (for

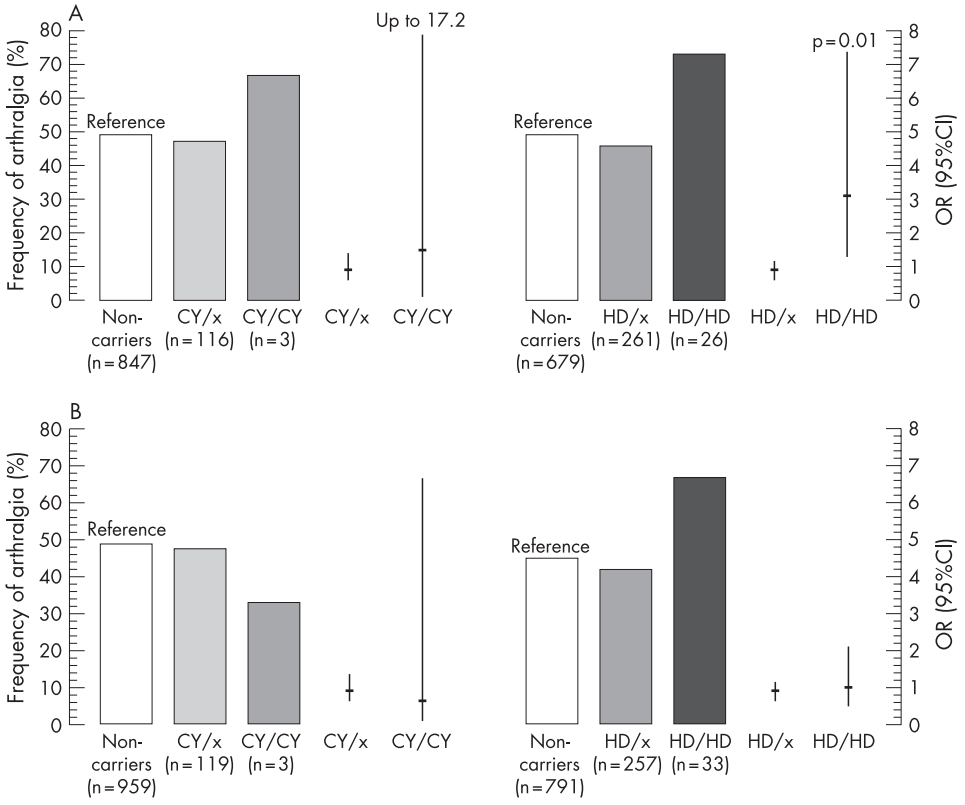


**Figure 1** Frequency of arthralgia in any joint site by *HFE* genotypes aged (A) ⩽65 years and (B) >65 years. Bars represent the frequency of arthralgia, and the vertical lines represent odds ratios. The secondary y axis represent odds ratios which compare the prevalence of arthralgia among subjects heterozygous or homozygous for the C282Y or H63D variants to that of non-carriers (ie, Reference), calculated using logistic regression analysis after adjustment for age and gender. Abbreviation: OR, odds ratio; 95% CI, 95% confidence interval; CY/x, C282Y heterozygotes; CY/CY, C282Y homozygotes; HD/x, H63D heterozygotes; HD/HD, H63D homozygotes

trend, p<0.01). Among subjects aged 65 years or younger, the number of joints with osteophytes was higher in H63D heterozygotes (p = 0.03) or homozygotes (p = 0.08) than in non-carriers (for trend, p = 0.03; table 3).

H63D homozygotes had a significantly increased number of hand joints with space narrowing, or radiographic osteoarthritis compared with non- carriers in subjects aged 65 years or younger. Again, no relation to *HFE* genotypes was found in subjects older than 65 years. We found no significant difference in the number of osteophytes, presence of space narrowing or radiographic osteoarthritis across *HFE* genotypes in either hip or knee joints (data not shown).

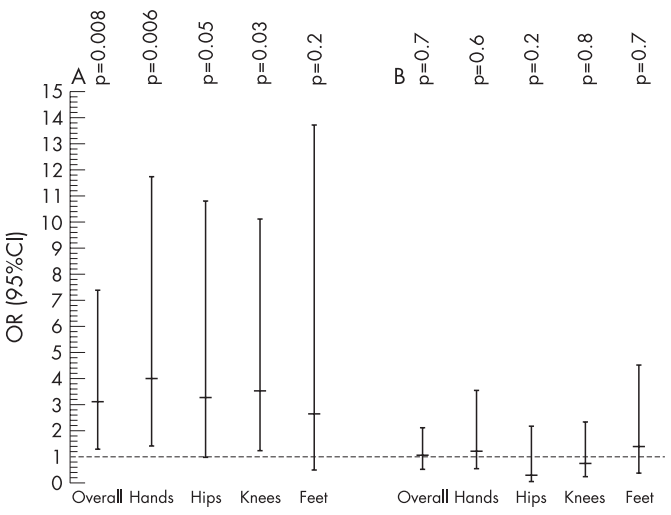


**Figure 2** Odds ratios for arthralgia in H63D homozygotes aged (A) ⩽65 years and (B) >65 years. The bars indicate the 95% confidence intervals.

### *HFE* variants and Heberden's nodes

Overall, 21.5% of H63D homozygotes (n = 51) compared with 16.9% of non-carriers (n = 1316) had Heberden's nodes (OR 2.1; 95% CI 1.1 to 3.9; p = 0.02). Again, H63D homozygotes aged 65 years or younger had a significantly (p = 0.02) higher frequency of Heberden's nodes compared with non-carriers (table 4).

### Compound heterozygotes and outcomes

Compound heterozygotes aged 65 years or younger were associated with none of the outcomes studied. Compound heterozygotes older than 65 years had a significantly higher frequency of polyarthralgia (2.9; 1.0 to 9.3; p = 0.05), and hip chondrocalcinosis (6.5; 1.8 to 22.3; p = 0.001) compared with non-carriers and had significantly more osteophytes in knee joints in the overall analysis (4.9 (0.6) vs 2.2 (0.1); p = 0.01) and in those older than 65 years (6.9 (1.2), n = 5 vs 2.4 (0.1), n = 374; p = 0.01). In hands, none of the outcomes studied showed any difference between compound heterozygotes and non-carriers in subjects older than 65 years.

### *HFE* variants, arthralgia and mortality

To explore why we found a strong relation of H63D homozygosity to arthralgia and arthropathy before age 65 years but not later in life, we studied the mortality in H63D homozygotes with arthralgia. In subjects aged 65 years or younger, H63D homozygotes with arthralgia were found to have a fourfold (95% CI 1.4 to 11.7; p<0.01) higher risk of mortality than non-carriers without arthralgia during the study's follow-up period.

### C282Y or H63D homozygotes and clinical arthropathy

When the rheumatologist (JH) re-examined the radiographs of all the C282Y (n = 6) or H63D (n = 59) homozygotes, most of the subjects had two or more joints affected with multiple pathologies such as osteophytes, sclerosis, joint space narrowing

**Table 1** Participants' characteristics by age and presence of arthralgia†

| | Age ⩽65 years | | Age >65 years | |
|---|---|---|---|---|
| | With arthralgia (n = 473) | No arthralgia (n = 493) | With arthralgia (n = 526) | No arthralgia (n = 555) |
| Age (years) | 60.3±0.1 | 60.4±0.1 | 71.2±0.2 | 70.8±0.2 |
| Women (% of total) | 58.9 | 41.1* | 63.7 | 42.7* |
| BMI (kg/m$^2$) | 26.1±0.2 | 26.3±0.2 | 25.9±0.2 | 26.3±0.2 |
| User of pain medicine or physiotherapy (%) | 69.8 | 30.2* | 68.7 | 31.3* |
| Frequency of *HFE* variants (%) | | | | |
| C282Y | 6.2 | 6.3 | 5.5 | 6.0 |
| H63D | 16.7 | 15.7 | 14.4 | 15.5 |

*Comparison between subjects with and without arthralgia p = 0.001; †Plus–minus values are means ± standard errors.
n, number of subjects.

and calcification. The clinical findings with regard to the features that we did not discuss earlier are summarised in table 5. In re-assessing the *x* rays of C282Y and H63D homozygotes for a clinical diagnosis, the rheumatologist (J H) was aware of the genotype, so an overestimation of clinical outcomes in this group is possible. Nevertheless, in only 3 subjects (3/65, 4.6%) were the radiographic findings recognised as compatible with hereditary haemochromatosis. Of the C282Y homozygotes, 3 subjects younger than 65 years had osteoarthritis in hands, and 1 of these had one total hip replacement. Of the other 2, 1 had mild generalised osteoarthritis, and another had a moderate spondylophytosis.

### *HFE* variants and clinical haemochromatosis

None of the C282Y or H63D homozygotes, or compound heterozygotes, had received a diagnosis of clinical haemochromatosis from their general practitioner or any other physician at the baseline or during the follow-up study period.

## DISCUSSION

### Principal findings

This study evaluated the relationship between *HFE* and arthropathy in the general population. Overall, we found that H63D homozygotes had arthralgia more often. In subjects aged 65 years or younger, H63D homozygosity was consistently associated with arthralgia in multiple joint sites, chondrocalcinosis, radiographic osteoarthritis in hands and Heberden's nodes. H63D homozygotes used pain medication more often. In subjects with arthralgia who were 65 years or younger at the baseline examination, H63D homozygotes had a higher mortality than non-carriers without arthralgia during the 11.4-year follow-up period. We found no association for C282Y homozygotes or heterozygotes. In subjects older than 65 years, compound heterozygosity was associated with arthralgia, chondrocalcinosis in hip joints and osteophytes in knee joints.

### Advantages and limitations of this study

A point of concern for population-based studies of genetic factors is the probability of bias due to population admixture.[31 32] Typing of multiple genetic markers as suggested by Pritchard and Rosenberg[33] has not revealed any evidence for the presence of population admixture in the Rotterdam Study. Another source of bias may be observer-related misclassification. All our radiographs were scored blind to other clinical data and genotyping. Further, any systematic loss to follow-up or missing data are unrelated to participants' *HFE* genotypes or osteoarthritis profile. Therefore, the occurrence of spurious associations due to population admixture or a selective misclassification is unlikely. The major strengths of our study are its population-based design, the large number of participants and the use of several related clinical and radiographic outcomes.

### C282Y, H63D and arthropathy

We observed that H63D homozygotes had a strong and consistent increased risk of early-onset arthralgia and arthropathy in multiple joint sites. In line with this finding, H63D homozygotes used pain medication more often in our study population. We found no relation to arthropathy in C282Y homozygotes or heterozygotes. The effect of C282Y on iron metabolism is stronger than that of H63D,[24 34] and so the risk for haemochromatosis is the highest.[15] Thus, one might expect a stronger association with arthropathy in C282Y carriers. There may be a number of explanations for why we failed to observe any association. One may speculate that the numbers of C282Y homozygotes were too few to draw any definite conclusion in our study. However, this lack of association is not unique to our population. Others have also found no relation to arthralgia or joint pathology in carriers of C282Y.[18–20] One of these studies comprises over 40 000 persons who were screened for *HFE* and showed no relation of arthralgia to C282Y homozygosity

**Table 2** Frequency of chondrocalcinosis in hip or knee joints by *HFE* genotypes

| | Age ⩽65 years | | | Age >65 years | | |
|---|---|---|---|---|---|---|
| *HFE* genotypes | n | Percent | Odds ratio (95% CI)† | n | Percent | Odds ratio (95% CI)† |
| C282Y | | | | | | |
| Non-carriers | 469 | 4.5 | 1.0 (reference) | 516 | 7.4 | 1.0 (reference) |
| Heterozygotes | 74 | 2.7 | 0.7 (0.1 to 2.9) | 60 | 8.3 | 1.2 (0.1 to 3.3) |
| Homozygotes | 2 | 0.0 | – | 2 | 0.0 | – |
| H63D | | | | | | |
| Non-carriers | 372 | 4.0 | 1.0 (reference) | 434 | 6.9 | 1.0 (reference) |
| Heterozygotes | 146 | 4.1 | 1.1 (0.4 to 2.8) | 147 | 10.2 | 1.8 (0.9 to 3.5) |
| Homozygotes | 14 | 21.4 | 4.7 (1.2 to 18.5)* | 19 | 0.0 | – |

*p = 0.02 for comparison with non-carriers; †OR, odds ratios compare the frequency of chondrocalcinosis among subjects heterozygous or homozygous for the C282Y or H63D variants with that of non-carriers, calculated using logistic regression analysis after adjustment for age and gender.
CI, confidence interval. n, number of subjects.

**Table 3** Number of hand joints with osteophytes, joint space narrowing or radiographic osteoarthritis (ROA) by *HFE* genotypes†

| | Osteophytes | | | | Joint space narrowing | | ROA‡ | |
|---|---|---|---|---|---|---|---|---|
| | ⩽65 years | | >65 years | | | | | |
| *HFE* genotypes | n | | n | | ⩽65 years | >65 years | ⩽65 years | >65 years |
| C282Y | | | | | | | | |
| Non-carriers | 590 | 5.0±0.3 | 534 | 6.3±0.4 | 1.4±0.1 | 1.6±0.2 | 2.4±0.5 | 3.3±0.4 |
| Heterozygotes | 78 | 5.5±0.6 | 71 | 5.8±0.7 | 1.9±0.3 | 1.2±0.4 | 2.3±0.4 | 2.6±0.6 |
| Homozygotes | 3 | 5.3±2.5 | 3 | 2.3±4.9 | 0.2±1.5 | 2.3±3.0 | – | 3.6±4.2 |
| H63D | | | | | | | | |
| Non-carriers | 466 | 4.4±0.3 | 446 | 4.7±1.6 | 1.0±0.1 | 2.0±1.0 | 2.0±0.2 | 3.5±1.4 |
| Heterozygotes | 184 | 5.2±0.4* | 142 | 4.7±1.7 | 1.2±0.2 | 1.6±1.0 | 2.4±0.3 | 3.2±1.4 |
| Homozygotes | 18 | 6.1±1.0 | 18 | 4.9±2.0 | 2.8±0.5** | 1.5±1.2 | 4.4±0.7** | 2.8±1.7 |

*p=0.03, **p=0.01 for comparison with non-carriers; †figures are means±standard errors, calculated using univariate linear regression analysis after adjustment for age and gender; ‡ROA was diagnosed for any joint with a Kellgren score 2 or higher.
n, number of subjects.

(n = 128) or compound heterozygosity (n = 616).[18] Together, these findings suggest that C282Y is not a determinant of arthralgia in the general population. When considering the relation between C282Y and joint pathologies, two studies reported a weak relation of C282Y to chondrocalcinosis,[22 35] and another study reported a relation between C282Y heterozygosity and late-onset hand osteoarthritis.[21] For C282Y heterozygosity, we found an effect on arthralgia and arthropathy only in compound heterozygotes for C282Y and H63D older than 65 years, suggesting that C282Y heterozygosity may have a late effect on arthropathy.

From a pathological prospect, this raises the question as to whether levels of iron determine the relation between H63D and early-onset arthropathy. In fact, iron overload may not be the main determinant of arthropathy, as it shows a poor response to phlebotomy,[2] and arthropathy did not show any relation to iron concentration in the liver[3] or to levels of serum iron or ferritin in our population (data not shown). Moreover, arthropathy can occur with moderate iron overload[1] and is uncommon in other forms of iron-storage diseases,[37] suggesting the arthropathy may not be explained directly by iron overload.[2 3 8] Further research is needed to determine the mechanism by which H63D affects the risk of arthropathy. The report on the relation between H63D and rheumatoid arthritis,[38] the consistent relation of H63D to polyarthralgia, Heberden's nodes, chondrocalcinosis and early-onset hand osteoarthritis, which are all partially inflammatory mediated conditions,[12 26 27 39] suggests that an alternative mechanism may be responsible. An understanding of the underlying aetiopathogenesis may provide new targets for intervention in haemochromatotic arthropathy.

## Clinical implications

In this study, H63D homozygosity was found to be associated with arthropathy. Earlier, we have shown that H63D homozygotes in the same study population had higher levels of serum iron and ferritin.[24] However, none of the H63D homozygotes had a clinical diagnosis of haemochromatosis, or of diabetes mellitus[40] or liver pathology, two diseases associated with haemochromatosis. This suggests that carriers of H63D may present initially with only arthropathy, perhaps together with excess iron. Thus, they may remain undiagnosed and therefore untreated for hereditary haemochromatosis. If left untreated, the disease may progress to irreversible complications like liver diseases[5] or to cerebro-cardiovascular events like stroke,[36 41] leading to early death. In this respect, the significantly higher mortality in a subgroup of H63D homozygotes with arthralgia aged 65 years or younger is of concern. Furthermore, the early mortality may explain why the association of H63D homozygosity to arthropathy is stronger early in life but absent later on. Further studies are needed, to translate our findings into clinical and public health practice.

## Conclusion

Taken together, our findings suggest that H63D may explain at least some of the early-onset arthropathy in the general population. Although this conclusion needs to be confirmed by others, we consider it may well be clinically relevant to test patients with arthralgia who are younger than 65 years for *HFE* variants.

## ACKNOWLEDGEMENTS

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**Table 4** Frequency of Heberden's nodes by *HFE* genotypes†

| | Age ⩽65 years | | | Age >65 years | | |
|---|---|---|---|---|---|---|
| *HFE* genotypes | n | Percent | Odds ratio (95% CI) | n | Percent | Odds ratio (95% CI) |
| | 701 | 19.7 | 1.0 (reference) | 835 | 19.2 | 1.0 (reference) |
| Heterozygotes | 107 | 15.0 | 0.9 (0.5 to 1.7) | 110 | 11.8 | 0.6 (0.3 to 1.0) |
| Homozygotes | 2 | 50.0 | 4.0 (0.2 to 65.3) | 2 | 0.0 | – |
| H63D | | | | | | |
| Non-carriers | 637 | 16.0 | 1.0 (reference) | 726 | 17.9 | 1.0 (reference) |
| Heterozygotes | 246 | 16.3 | 1.0 (0.7 to 1.6) | 240 | 19.6 | 1.1 (0.7 to 1.6) |
| Homozygotes | 23 | 34.8 | 3.1 (1.3 to 12.8)* | 28 | 25.0 | 1.4 (0.6 to 3.5) |

*p<0.02 for comparison with non-carriers; †OR, odds ratios compare the frequency of Heberden's nodes among subjects heterozygous or homozygous for the C282Y or H63D variants to that of non-carriers, calculated using logistic regression analysis after adjustment for age and gender.
CI, confidence interval. n, number of subjects.

**Table 5** Radiographic findings (%) in subjects homozygous for the *HFE* C282Y or H63D variants*

| | Age ⩽65 years | | | | Age >65 years | | | |
|---|---|---|---|---|---|---|---|---|
| **Radiographic findings** | **Hips** | **Knees** | **Hands** | **Spine** | **Hips** | **Knees** | **Hands** | **Spine** |
| C282Y homozygotes (n = 6) | | (n = 3) | | | | (n = 3) | | |
| Spondylophytes | – | – | – | 100.0 | – | – | – | 100.0 |
| Articular or peri-articular calcifications | 33.3 | 33.3 | 0.0 | 0.0 | 0.0 | 33.3 | 0.0 | 0.0 |
| Subchondral bony sclerosis | 33.3 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Subchondral bony cysts | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| H63D homozygotes (n = 59) | | (n = 25) | | | | (n = 34) | | |
| Spondylophytes | – | – | – | 96.0 | – | – | – | 50.0 |
| Articular or peri-articular calcifications | 20.0 | 16.0 | 20.8 | 16.0 | 0.0 | 6.0 | 37.0 | 13.3 |
| Subchondral bony sclerosis | 16.0 | 4.0 | 20.8 | 12.0 | 17.9 | 0.0 | 29.6 | 6.6 |
| Subchondral bony cysts | 8.0 | 0.0 | 4.0 | 0.0 | 0.0 | 3.0 | 14.3 | 0.0 |

*Figures are percentages.
n, number of subjects.

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